REMARKS

Claim status

Claims 8-29 are pending and stand rejected. Claim 11 is amended to correct an inadvertent typographical error. Applicants respectfully submit that the instant amendments introduce no new matter.

Telephonic interview

Applicants wish to thank the Examiner for granting a telephonic interview on September 23, 2009. The interview was conducted by Applicants' representatives in conjunction with Dr. Timothy P. Clackson and David Berstein, Esq. (Chief Scientific Officer and Chief Intellectual Property Officer, respectively at ARIAD Pharmaceuticals, Inc., licensee of the present application). During the interview, the Connolly et al.[1] reference, which formed the basis of the Examiner's new rejections, was discussed. In particular, Dr. Clackson discussed the experiments that are described in Connolly and explained their limitations. The Examiner indicated that it would be helpful if Applicants presented Dr. Clackson's points in a declaration under 37 C.F.R. § 1.132. Applicants are therefore submitting a suitable declaration herewith.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 8-29 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner had previously rejected these claims on the same basis in the final Office Action that was mailed on July 15, 2005. After an appeal, the Board of Patent Appeals and Interferences (the "Board") rendered a decision that was mailed on October 1, 2008 (hereinafter the "Decision") reversing, among other things, this written description rejection. A notice of allowance was mailed on December 2, 2008. Applicants then filed a request for continued examination on March 2, 2009 along with an Information Disclosure Statement that cited *inter alia* references that had come to Applicants' attention in connection with opposition proceedings for a related European application.

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[1] Connolly *et al.*, "Synthesis and Erythropoietin Receptor Binding Affinities of *N,N*-Disubstituted Amino Acids," *Bioorganic & Medicinal Chemistry Letters*. 10:1995-1999 (2000), hereinafter "Connolly", submitted with the Information Disclosure Statement filed on March 2, 2009.

The Examiner has reinstated the written description rejection, repeating arguments that were already considered by the Board, but adding remarks in relation to Connolly, one of the references that was submitted with the Information Disclosure Statement on March 2, 2009. For example, the Examiner repeats an argument that, essentially, asserts that a structure-function relationship is required to show that Applicants were in possession of the claimed genus:

> "Applicant claims the agent by function only, whereby the agent causes the oligomerization of two or more protein mediators in a manner which effects a biological event mediated by association of two or more endogenous cell surface receptor [*sic*], without any disclosed or known correlation between the structure of the agent and the protein mediators [...] The simple fact is that the skilled artisan could not envision how to activate hypothetical Signal Cascade 'X' based on the instant specification because there is no description of what genus of agents will oligomerize hypothetical Receptor 'X.' Based on the teachings of the specification, the skilled artisan cannot envision the broad genus of agents to be made in the claimed method because the skilled artisan cannot envision which agents will bind to and effect a biological event for any given protein mediators (e.g., cell surface receptors)" (paragraph bridging pages 3-4 of the current Office Action).

Applicants note that this argument was presented in previous Office Actions and was therefore part of the record before the Board. In particular, in the Examiner's Answer of January 1, 2007, the Examiner argued that there is:

> "[...] no description of even a single compound that is comprised of two non-peptidic moieties that each bind to a cell surface receptor, or endogenous protein mediator, where the agent can effect a biological event mediated by the association of the two receptors or endogenous protein mediators [...] [T]he skilled artisan cannot envision a sufficient number of agents which include two non-peptide moieties that bind to cell surface receptors or endogenous protein mediators, wherein the compounds have the ability to effect a biological event mediated by the association of the two cell surface receptors or endogenous protein mediators. There is no description of a structural feature that correlates with the functional ability of an agent to bind two cell surface receptors, or two endogenous protein mediators in a manner which results in an effect on a biological event mediated by the association of said receptors or endogenous protein mediators [...]" (page 4 of the Examiner's Answer).

This very passage was quoted in the Board's Decision (see pages 5-6 of the Decision). Yet, after considering the Examiner's arguments, Applicants' arguments, the

knowledge in the art, and the disclosure in the present specification, the Board decided that:

> "[…] the Specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, [Applicants] were in possession of the invention as claimed" (sentence bridging pages 8 and 9 of the Decision).

In reaching this conclusion, the Board rejected the idea that a structure-function correlation is required in all cases to satisfy the written description requirement, noting that:

> "It has been held that a claimed DNA could be described without, necessarily, disclosing its structure. *See Enzo Biochem Inc. v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002). Our appellate review court has also noted that '*Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.' *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003)" (page 8 of the Decision).

In the current Office Action, the Examiner seems to take the position that the Board would alter its decision based solely on the disclosure provided by Connolly. Specifically, the Examiner asserts that Connolly "teaches […] that the compounds […] tested had high affinity for the EPO receptors, but failed to show EPO-mimetic activity as expected" (see page 6 of current Office Action). The Examiner then argues that "it is apparent that the relationship of structure of a small, non-peptidic molecule to its function in dimerization, even where affinity is high for one subunit of the receptor at a time, was not well enough understood at the time of filing to have permitted one of skill to have recognized that Applicants were in possession of the full scope of the claims" (see page 6 of current Office Action).

Applicants respectfully traverse this new rejection and submit that the Board would not alter its decision based solely on the disclosure of Connolly. As described by Dr. Clackson during the interview and in the declaration filed herewith, Connolly describes an incomplete and consequently flawed set of experiments that are not representative of the expected level of skill in the relevant field at the time. In particular, the experiments were performed in such a way that one cannot conclude that the compounds they tested even bound the EPO receptors in their cell-based proliferation assay. Indeed, Connolly only demonstrated EPO receptor binding in a cell-

free *in vitro* assay. Having obtained what Connolly interpreted as negative results in the cell-based proliferation assay, Connolly did not perform control experiments that would have determined whether the compounds actually bound the EPO receptors as presented on a cell. As explained in the declaration, one of ordinary skill in the art would have considered such a control experiment necessary to adequately interpret the negative-seeming results from the cell proliferation assay. Thus, the results Connolly observed could easily reflect a failure of the compounds to bind to EPO receptors as presented on cells rather than from a failure to activate after hypothetical binding. In the absence of binding, the disclosure of Connolly sheds little if any new light on issues relevant to the instant case.

Besides failing to include adequate controls to confirm binding, Connolly also failed to perform routine experiments to exclude the possibility that their choice of linkers – which, although "convenient", had well-understood handicaps – was a poor experimental design choice for making a scientific contribution on dimerizer-related signaling. In particular, Connolly chose four closely related, obviously hydrophobic linkers, and after having obtained an apparent experimental failure, made no effort to check their results using any other linker. It is entirely plausible that any of a wide variety of alternative linkers would have produced an active dimeric compound using the same monomeric EPO receptor ligands (although it is not at all clear that their activity would be identified using Connolly's methodology or in fact that Connolly's compounds weren't themselves active, as discussed below). It would have been considered routine and well within the skill in the art to test a diverse set of linking groups, especially after an apparent experimental failure. Again, a possibly improvident choice of linker, coupled with a failure to do the routine checking commensurate with the skill in this art, sheds little or no relevant light on the issues at hand.

Turning to Connolly's read-out, it is important to note that Connolly fails to specify the concentration at which the dimeric compounds were tested, let alone whether the compounds were tested at a variety of concentrations. As discussed in the declaration, it is completely possible that Connolly was simply operating at a concentration that was either too low or too high for a biologically active dimerizing agent to score positive in the cell-based assay. Applicants therefore respectfully submit that in the absence of such routine control experiments to confirm and characterize the results, it would be improper to give Connolly undue weight when considering whether the present application satisfies the written description requirement.

To highlight the more characteristic level of routine experimental rigor in the art, to contrast the deficiencies in the Connolly disclosure, and as a reminder of the overwhelmingly encouraging results in the other references of record, the Examiner is referred to those references, and in particular, to those dealing with the EPO receptor that were prior to or roughly contemporaneous with Connolly. For example, a year before Connolly was published, Qureshi et al.[2] reported successful activation of the EPO signaling pathway via dimerization of the same EPO receptor. Notably, Qureshi performed cell-based activation assays at different dimerizer concentrations and observed a sharp drop off at high concentrations: "[t]he decrease in the luciferase activity observed at higher concentrations of compound 5 may be caused by toxicity or by the engagement of EPOR in a 1:1 (EPOR/compound) complex, thus preventing the formation of EPOR dimers needed for the activation of the JAK/STAT pathway" (see page 12159, column 2; see also Figure 4). Goldberg et al.[3] also reported successful activation of the EPO signaling pathway via dimerization of the EPO receptor. In contrast to Connolly, Goldberg began with a diverse set of monomeric compounds and combined these with an equally diverse set of linkers to produce test dimerizers. For example, Figure 2 shows the building blocks of an initial iminodiacetic library of 600 C2-symmetrical compounds. Figure 4 shows a series of 109 structurally diverse primary and secondary amines used to prepare derivatives of compounds in the initial iminodiacetic library. Figure 6 shows structures of 77 amine subunits used to prepare even further analogues of the initial iminodiacetic library. Higher order (e.g., trimers and tetramers) libraries were also synthesized, as was a completely different dimeric library, an isoindoline library of 1000 compounds. A person of ordinary skill in the art would recognize that the construction and screening of these libraries is a matter of routine experimentation. Furthermore, a variety of linkers were tested to optimize the dimers. See, for example, the ten different R3 linking groups (C1-C10) shown at the bottom of Figure 2, the nine additional R3

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[2] Qureshi *et al.*, "Mimicry of erythropoietin by a nonpeptide molecule," *Proceedings of the National Academies of Sciences*, 96(21):12156-12161 (1999), hereinafter "Qureshi", submitted with the Information Disclosure Statement filed on March 2, 2009.

[3] Goldberg *et al.*, "Erythropoietin Mimetics Derived from Solution Phase Combinatorial Libraries," *Journal of the American Chemical Society*, 124(4):544-555 (2002), hereinafter "Goldberg", submitted with the Information Disclosure Statement filed on March 2, 2009.

linking groups shown in Figures 8 and 9 (C11-C19), and the ten different R3 linking groups shown in Figure 12 (C1′-C10′). Goldberg also performed dose response curves to obtain optimal concentration ranges of effective compounds (see Figure 13). These contemporary teachings highlight quite clearly the routine experiments that Connolly should have performed before making a statement, or supporting a conclusion, on the technology.

In this context, Applicants note that the present specification provides ample guidance to one of ordinary skill in the art as to how to perform experiments that were omitted in Connolly. For example, whereas Connolly failed to test their dimeric compounds for their ability to bind receptors in a cell-based assay, the specification provides that "[…] covalently linked dimerizers will usually be tested (e.g., as above) to confirm retention of binding capability with respect to each of the proteins of interest and/or in cell-based assays as described below" (see page 21, lines 5-8). Of note, the section of the specification that discusses binding assays (pages 15-19) describes using cell-free and cell-based assays (e.g., see page 16, lines 9-12 and page 17, lines 17-28). In contrast to the four linkers that limit the scope and meaning of Connolly's work, the specification describes a diverse array of linkers that could be used in routine optimization experiments (see page 19, line 11 through page 20, line 29), provide illustrative examples in the compounds on pages 24-25 and citations to other relevant information in the patent and scientific literature (on page 23 and elsewhere).

For all these reasons, Applicants respectfully submit that the Board would not give much weight to Connolly and would therefore not change its judgment because of Connolly. Applicants therefore respectfully submit that the written description rejection should be withdrawn.

Claims 8-29 also stand rejected under 35 U.S.C. § 112 as allegedly failing to comply with the enablement requirement. Though this rejection is presented as a new rejection, the Examiner relies on similar arguments to those that were used to support the written description rejection and that were before the Board. For example, the Examiner argues that the specification is lacking because it fails to describe dimerizing agents that were later described by Qureshi et al. and Tian et al.[4] In this case, the Examiner deems that the alleged lackings of the specification

[4] Tian *et al.*, "A small, nonpeptidyl mimic of granulocyte-colony-stimulating factor ," *Science*, 281:257-259 (1998), hereinafter "Tian," submitted with the Information Disclosure Statement filed on March 2, 2009.

constitute a failure to meet the enablement requirement:

> "[I]n post-filing art (Qureshi and Tian, as recited above), novel agents that were not described in the instant specification were identified as having the capacity to oligomerize and activate a signal transduction cascade. Neither of these agents are taught by the instant specification, nor is there a teaching that agents having a similar structure would activate a signal transduction cascade via any protein mediator" (page 8 of current Office Action);
>
> and
>
> "[T]he ordinary skilled artisan would be required to empirically identify a vast number of agents for each receptor and heterologous combinations thereof, and determine which agents corresponded to which receptor combinations for activation of the respective signaling cascade [...] This is evidenced by the post-filing art, wherein two groups (Qureshi and Tian) had to identify compounds de novo, in order to oligomerize a particular receptor to induce a signaling cascade. Importantly, the compounds identified in Qureshi and Tian are not described in the instant specification or the art at the time of filing [...] This demonstrates that undue and unpredictable trial and error experimentation would be required to practice the claimed invention, because agents that were not even identified in the instant specification or the art at the time of filing are needed to practice the claimed invention. If the agents to practice the invention must still be identified, then it is impossible for the skilled artisan to use an invention that requires the identity of the agent" (pages 10-11 of current Office Action).

Although these arguments were not previously packaged as an enablement rejection, and the Board had formally reviewed a written description rejection, their Decision addressed the state of the art and the level of the unpredictability:

> "We do not find that the Examiner has given appropriate weight to the state of knowledge in the field of the invention [...] [w]e do not find that the Examiner has properly characterized the level of unpredictability in the art" (page 10 of the Decision).

As with the written description rejection, it appears that the Examiner is taking the position that the Board would alter its analysis with respect to the level of predictability in the art solely in light of the disclosure of Connolly. For the same reasons that were discussed above and in the declaration submitted herewith, the purported negative results that are described by Connolly should not be given undue weight in determining the level of predictability in the art, at or subsequent to the time of filing. Applicants respectfully submit that the Board's conclusions

regarding the state of the art would therefore apply equally to the enablement rejection in the present application. Applicants therefore respectfully submit that the enablement rejection should also be withdrawn.

Conclusion

In view of the above remarks, the telephonic interview, and the declaration by Dr. Clackson submitted herewith, Applicants respectfully request that the Examiner reconsider and withdraw the outstanding rejections. Favorable action in the form of a Notice of Allowance is believed to be next in order, and such an action is earnestly solicited. It is believed that all fees due with this response are being submitted herewith. If any additional fees *necessary* to keep the present case pending and/or to protect the filing date are due, or any overpayment has been made, authorization is hereby given to charge or credit Deposit Account No. 03-1721 for any deficiencies or overages in connection with this response. No authorization is permitted to charge "optional" fees, *e.g.*, excess claims fees. In any event wherein the USPTO believes that additional fees are due, a Notice to that effect is respectfully requested.

Respectfully submitted,

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